

Do the Level of Nodal Disease According to the TNM Classification and the Number of Involved Cervical Nodes Reflect Prognosis in Patients With Differentiated Carcinoma of the Thyroid Gland?

NOBUAKI SATO, MD,^{1*} MANABU OYAMATSU, MD,¹ YU KOYAMA, MD,¹ IWA O EMURA, MD,² YOICHI TAMIYA, MD,¹ AND KATSUYOSHI HATAKEYAMA, MD¹

¹Department of Surgery, Niigata University School of Medicine, Niigata, Japan

²Department of Pathology, Niigata University Medical Hospital, Niigata, Japan

Background and Objectives: The importance of nodal involvement as a prognostic factor in differentiated carcinoma of the thyroid gland remains controversial. We therefore attempted to confirm the prognostic factors in differentiated thyroid carcinoma, with special reference to nodal status.

Patients and Methods: A total of 139 patients with differentiated thyroid cancer followed for 2–27 years, with a median follow-up of 7 years were studied. All patients underwent surgical resection, either subtotal, total, or lobectomy, with modified radical neck dissection. Survival was calculated using the Kaplan–Meier method.

Results: Ten (7%) patients have died from thyroid cancer. Adverse prognostic factors included age >45 years ($P = 0.0120$), the presence of distant metastases ($P = 0.0006$), and TNM stage ($P = 0.0002$). The number of lymph nodes dissected ranged from 6 to 92, with an average of 26. Lymph node metastases were found in 102 (73%) patients. There was no difference in survival according to the level of nodal disease by the TNM classification. Furthermore, the number of cervical lymph nodes involved had no effect on the survival.

Conclusion: Our results suggest that the presence of histologically confirmed lymph node metastases is not an important prognostic factor in patients with differentiated thyroid carcinoma.

J. Surg. Oncol. 1998;69:151–155. © 1998 Wiley-Liss, Inc.

KEY WORDS: thyroid gland; differentiated thyroid carcinoma; cervical lymph node; prophylactic lymph node dissection

INTRODUCTION

Several reviews of large numbers of patients have identified the prognostic factors in differentiated carcinoma of the thyroid gland [1–4]. Lymph node metastases at presentation are common in papillary thyroid cancer. It has not been established whether the presence of lymph node metastases in differentiated thyroid carcinoma implies poor prognosis [5]. For papillary thyroid cancer, lymph node metastases at presentation do not seem to affect survival adversely, but do increase the risk of lo-

coregional tumor recurrence. By contrast, in follicular thyroid cancer, nodal metastases at presentation may adversely affect cause-specific mortality but, because of their rarity, definite conclusions are impossible [6]. Rossi et al. [7] have reported the discontinuation of the use of

*Correspondence to: Nobuaki Sato, MD, Department of Surgery, Niigata University School of Medicine, 1-757 Asahimachi-dori, Niigata, Niigata 951-8520, Japan. Fax No: (81) 25-227-0779.
E-mail: nobus@med.niigata-u.ac.jp

Accepted 4 September 1998

prophylactic nodal dissection and the progressive replacement of radical neck dissection by modified radical neck dissection and that conservative surgical therapy of well-differentiated carcinoma of the thyroid can be effective with minimal complications. In other types of cancer, not only the presence or absence of lymph nodes metastases, but also the level of the metastases, is an important prognostic parameter. Many studies have clarified the prognostic significance of positive nodes in breast and colorectal cancer [8,9]. Most of the larger studies have used dissection of obviously involved nodes [2,3]. This paper describes our experience with patients with differentiated thyroid cancer undergoing systematic cervical lymph nodes dissection, which enabled us to evaluate the status of pathologic lymph nodes more precisely. The aim of the study was to confirm prognostic factors, with special reference to nodal status, in patients with differentiated thyroid carcinoma.

PATIENTS AND METHODS

We retrospectively reviewed the charts of 182 patients with the diagnosis of carcinoma of the thyroid treated in the Niigata University Medical Hospital between 1970 and 1995. Patient records were reviewed with respect to presentation, management, and outcome. The follow-up period ranged from 2 to 27 years, with a median of 7 years. The study had the disadvantages of any retrospective analysis; as a result, pathologic and clinical details were incomplete for some patients. Patients with a diagnosis of sclerosing papillary cancer were excluded from the study. Patients were eligible for the study if they had undergone a modified radical neck dissection along with the thyroid resection. We studied the records of 139 patients (124 women, 15 men) with differentiated thyroid carcinoma. A total of 110 papillary carcinomas and 29 follicular carcinomas were identified. The patients' ages ranged from 12 to 78 years, with an average of 48 years.

All patients underwent surgical resection of the thyroid gland, either subtotal ($n = 64$), total ($n = 43$), or lobectomy ($n = 32$), with or without isthmusectomy. We perform systematic lymphadenectomy in patients with differentiated thyroid cancer. Thyroidectomy along with lymph node dissection of the central cervical compartment was performed first, preserving the recurrent laryngeal nerves and external laryngeal nerves. The lateral jugular or cervicollateral lymph nodes were resected ipsilaterally by the method of modified radical neck dissection, preserving the internal jugular vein, sternocleidomastoid muscle, and accessory nerve. The resected specimens of the thyroid gland and the dissected lymph nodes were fixed in 10% formalin. Permanent paraffin sections were stained routinely by hematoxylin and eosin (H&E). The number of lymph nodes excised, and those involved by the disease, were documented quantitatively by histologic analysis. In this study, the number of lymph

nodes dissected ranged from 6 to 92, with an average of 26. In order to evaluate the prognostic significance of the level of metastases, only those patients in whom the number of cervical nodes dissected was 6 or more were included in this study.

Six widely accepted risk factors possibly influencing survival were selected for analysis: age at diagnosis; gender; primary tumor size; extrathyroidal extension; tumor, node, metastases (TNM) stage according to the International Union Against Cancer (UICC) in 1997 [10]; and the presence or absence of cervical lymph node metastases.

Survival rate were calculated using the Kaplan–Meier method and evaluated by the log-rank test or generalized Wilcoxon test. The numbers are expressed as the mean and standard deviation. The Wilcoxon–Mann–Whitney test was applied to prove mean differences between two groups, and analysis of contingency tables was done with the chi-square test. *P*-values were derived from two-tailed tests. Differences were considered significant when $P < 0.05$.

RESULTS

The recurrence rate was 34 of 139 (24.5%). Recurrences were classified as local if they involved the thyroid bed, trachea, esophagus, midline of the neck in the thyroid region, or nodes of the neck near the previous neck dissection. They were classified as distant if they were outside the neck region. If disease appeared in more than one location simultaneously, it was defined as the most serious metastatic site for the purpose of analysis. Local recurrences were found in 17 (12%) of the 139 patients. Distant metastases were identified in 17 (12%) of the 139 patients, including the bone, lung, liver, and brain. Of the 17 patients with local recurrence, 13 had papillary carcinoma. Distant metastases developed in 6 of the 17 patients with follicular carcinoma. Ten (7%) of the 139 patients have died of thyroid cancer.

Age at diagnosis, the presence of distant metastases, and TNM stage had a significant influence on survival ($P = 0.0006$ and $P = 0.0002$) (Table I). When T categories were compared, extrathyroidal invasion was not an important factor influencing survival.

Lymph node metastases were found in 102 (73%) of the 139 patients. There was no significant difference in the number of positive node metastases between survivors and nonsurvivors (4.8 ± 5.5 vs. 4.5 ± 6.4). The level of lymph node metastases according to the TNM classification had no effect on survival (Fig. 1). Furthermore, no difference in survival was found according to the number of cervical nodes involved (Fig. 2).

DISCUSSION

Neither the level of nodal disease according to the TNM classification, nor the number of positive nodes

TABLE I. Univariate Analysis of Clinicopathologic Factors in Patients With Differentiated Thyroid Cancer

Variable	No. of patients	Survival rate (%)		P
		5 yr	10 yr ^b	
Age (years)				
<45	54	100	100	0.0120
≥45	85	92	88	
Gender				
M	15	71	71	0.5995 (ns) ^f
F	124	93	90	
Primary tumor (pT) ^a				
pT1	8	100	100 ^c	0.3157 (ns)
pT2	56	98	91	
pT3	35	82	82	
pT4	40	87	87	
Extrathyroid extension				
Yes	36	92	92	0.7803 (ns)
No	103	90	87	
Distant metastases				
Yes	9	44	—	0.0006
No	130	94	91	
Staging group				
Stage I	58	100	100	0.0002
Stage II	18	94	71 ^d	
Stage III	55	88	88	
Stage IV	8	30	—	
No. of positive nodes				
0	37	89	81	0.8664 (ns)
1–3	38	93	93	
4–10	42	90	90	
>11	22	91	91 ^e	
Level of positive nodes (pN) ^a				
pN0	37	89	81	0.0519 (ns)
pN1a	49	100	100	
pN1b	53	83	83	

^aRefer to the TNM system [10] for details.^bSurvival rates beyond 10 years are indicated.^c15 years.^d14 years.^e18 years.^fns, not significant.

affected the prognosis of patients with differentiated thyroid cancer. We have also confirmed that the factors determining survival in patients with differentiated thyroid cancer are age at diagnosis, the presence or absence of distant metastases, and the TNM stage. Intraoperative sampling of nodes is potentially the most accurate way of assessing the extent of lymphatic tumor spread. When more extensive dissection is undertaken, more than 70% of patients are found to have nodal involvement [11–13]. Nevertheless, few studies take the level of nodal involvement according to TNM classification into consideration in evaluating the prognostic significance of the nodal status. We believe that our results reflect the status of lymph node involvement precisely, as the patients underwent a modified radical neck dissection, and six or more lymph nodes were removed and examined histopathologically.

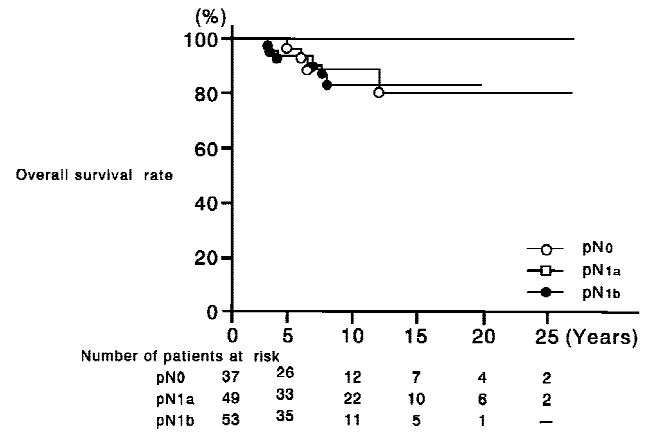


Fig. 1. Overall survival of patients with differentiated thyroid carcinoma, grouped according to the level of positive nodes. pN0, No regional lymph node metastases; pN1a, metastases in ipsilateral cervical lymph nodes; pN1b, metastases in bilateral, midline, or contralateral cervical or mediastinal lymph nodes.

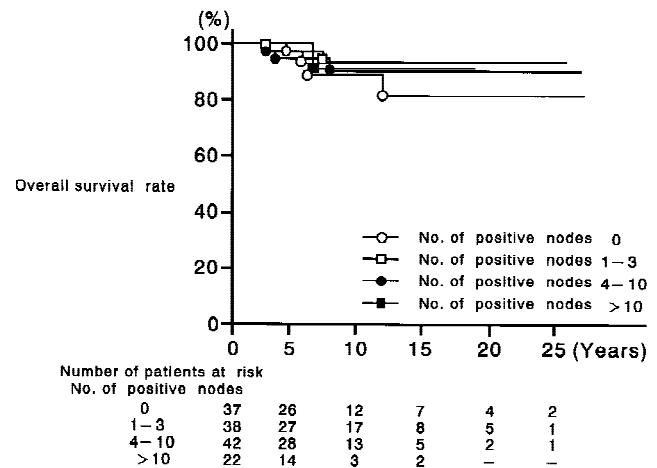


Fig. 2. Overall survival of patients with differentiated thyroid carcinoma, grouped according to the number of positive nodes.

There is considerable controversy concerning not only the indications for, but also the extent of cervical lymph node dissection in well-differentiated thyroid cancer. The necessity for regional lymph node dissection in the absence of clinically involved nodes remains a controversial issue. Some physicians advocate prophylactic lymph node dissection because of the high incidence of cervical node involvement [11,14]. They argue that a wait-and-see policy may require reoperation, with an associated higher morbidity.

However, there seems to be no justification for the prophylactic removal of regional lymph nodes in patients with papillary carcinoma of the thyroid gland. Modified radical neck dissection may be beneficial if clinically suspected regional lymph nodes are present in the lateral part of the neck. A discrepancy exists between the presence of microscopic foci of thyroid cancer in the cervical

lymph nodes and the observed nodal recurrence rate [15]. In the study by Noguchi et al. [16], among those patients operated on before 1962 and judged not to have metastases and who did not undergo lymph node excision, 83% were assumed to have undiagnosed metastases. Survival without recurrence in those patients considered free from metastases was as high as 77% after 15 years. No malignant biologic effect has been demonstrable in those patients in whom metastatic deposits were microscopic [16]. Hamming [17] retrospectively evaluated the management of two groups of patients with papillary carcinoma of the thyroid gland. When a more extensive search was carried out, more metastases of the lymph nodes were discovered. However, most of these occult metastases appear to regress or remain in a dormant state. This raises the question of whether the biologic and prognostic significance of nodal metastases found incidentally during systematic dissection is the same as for more obviously involved nodes. The question is how many such metastases would ever become clinically evident.

The present study has some limitations because of the relatively small number of patients, the short median follow-up of 7 years, and the absence of a multivariate life-curve analysis. Hay et al. [18] reported that survival is not influenced by the extent of thyroid resection in low-risk patients, while only a trend toward improved survival with bilateral lobar resection, compared with unilateral resection, is observed in high-risk patients. These investigators have reported that local recurrence rates after unilateral lobectomy are significantly higher than after total thyroidectomy [19]. Although the extent of resection varied from lobectomy to total thyroidectomy in our study, it is unlikely that the degree of thyroid resection had a significant influence on survival. There is a virtual consensus that a lobectomy is the procedure of choice for well-differentiated thyroid carcinoma limited to one lobe [20]. Regional nodes are more commonly involved by thyroid cancer in the young [13]. Older patients have been found to have a poorer prognosis than that of younger patients with thyroid cancer [21]. Thus, the adverse effect of regional lymph node involvement is masked if a group of patients is analysed that includes relatively few elderly patients with involved nodes. Further studies are needed to determine whether prophylactic cervical lymph node dissection leads to better results in the treatment of elderly patients with differentiated thyroid carcinoma.

In the treatment of cancer, only well-evaluated data from prospective randomized trials are acceptable for decision as to whether one treatment is more effective than another. We were unable to show any prognostic significance for nodal disease in patients with differentiated thyroid cancer in this study. The systematic excision of regional lymph nodes appears to be of no benefit in patients with no gross nodal involvement at surgery. It

is likely that delaying lymphadenectomy until nodal disease is clinically demonstrable will not have a negative impact on survival. This approach also avoids surgical morbidity in patients who never manifest a nodal failure despite the development of distant metastases. The surgical approach to differentiated thyroid carcinoma should be individualized on the basis of prognostic factors and risk group analysis [18,22,23].

CONCLUSION

Our study confirms that the factors determining survival in patients with differentiated thyroid cancer are age at diagnosis, the presence of distant metastases, and stage according to the TNM classification. Although the number of patients in our study was small, it suggests that both the number and the level of the nodal involvement according to the TNM classification do not accurately reflect prognosis in patients with differentiated thyroid cancer. The impact of modified radical neck dissection on survival must be proved by further evaluation.

ACKNOWLEDGMENT

The authors thank Yayoi Sato, MD, for helpful suggestions in writing this article.

REFERENCES

1. Cady B, Sedgwick CE, Meissner WA, et al.: Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. *Ann Surg* 1976;184:541-553.
2. Simpson WJ, McKinney SE, Caruthers JS, et al.: Papillary and follicular thyroid cancer-prognostic factors in 1,578 patients. *Am J Med* 1987;83:479-488.
3. Samaan NA, Schultz PN, Hickey RC, et al.: The results of various modalities of treatment of well differentiated thyroid carcinoma: A retrospective review of 1,599 patients. *J Clin Endocrinol Metab* 1992;75:714-720.
4. Loree TR: Therapeutic implications of prognostic factors in differentiated carcinoma of the thyroid gland. *Semin Surg Oncol* 1995;11:246-255.
5. Bacourt F, Asselain B, Savoie JC, et al.: Multifactorial study of prognostic factors in differentiated thyroid carcinoma and a re-evaluation of the importance of age. *Br J Surg* 1986;73:274-277.
6. Grebe SK, Hay ID: Thyroid cancer nodal metastases: Biologic significance and therapeutic considerations. *Surg Oncol Clin North Am* 1996;5:43-63.
7. Rossi RL, Cady B, Silverman ML, et al.: Current results of conservative surgery for differentiated thyroid carcinoma. *World J Surg* 1986;10:612-622.
8. Barth RJ Jr, Danforth DN Jr, Venzon DJ, et al.: Level of axillary involvement by lymph node metastases from breast cancer is not an independent predictor of survival. *Arch Surg* 1991;126:574-577.
9. Fisher ER, Sass R, Palekar A, et al.: Dukes' classification revised; findings from the National Surgical Adjuvant Breast and Bowel Projects (Protocol R-01). *Cancer* 1989;64:2354-2360.
10. UICC International Union Against Cancer: TNM Classification of Malignant Tumors. 5th Ed. New York: Wiley-Liss, 1997:47-50.
11. Noguchi M, Kumaki T, Taniya T, Miyazaki I: Bilateral cervical lymph node metastases in well-differentiated thyroid cancer. *Arch Surg* 1990;125:804-806.
12. Attie JN, Khafif RA, Steckler RM: Elective neck dissection in papillary carcinoma of the thyroid. *Am J Surg* 1971;122:464-471.
13. Tisell LE, Nilsson B, Molne J, et al.: Improved survival of patients

- with papillary thyroid cancer after surgical microdissection. *World J Surg* 1996;20:854–859.
14. Ozaki O, Ito K, Kobayashi K, Suzuki A, Manbe Y: Modified neck dissection for patients with nonadvanced, differentiated carcinoma of the thyroid. *World J Surg* 1988;12:825–829.
15. Cline RE, Shingleton WW: Long-term results in the treatment of carcinoma of the thyroid. *Am J Surg* 1968;115:545–551.
16. Noguchi S, Noguchi A, Murakami N: Papillary carcinoma of the thyroid. II. Value of prophylactic lymph node excision. *Cancer* 1970;26:1061–1064.
17. Hamming JF: Preoperative diagnosis and treatment of metastases to the regional lymph nodes in papillary carcinoma of the thyroid gland. *Surg Gynecol Obstet* 1989;169:107–114.
18. Hay ID, Grant CS, Taylor WF, et al.: Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: A retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery* 1987;102:1088–1095.
19. Hay ID, Grant CS, van Heerden JA, et al.: Papillary thyroid microcarcinoma: A study of 535 cases observed in a 50-year period. *Surgery* 1992;112:1139–1147.
20. Buckwalter JA, Thomas Jr CG: Selection of surgical treatment for well differentiated thyroid carcinomas. *Ann Surg* 1972;176:565–578.
21. McDermott WV, Morgn WS, Hamlin E Jr, et al.: Cancer of the thyroid. *J Clin Endocrinol Metab* 1954;14:1336–1354.
22. Cady B, Rossi R: An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery* 1988;104:947–953.
23. Byar DP, Green SB, Dor P, et al.: A prognostic index for thyroid carcinoma. A study of the EORT thyroid cancer cooperative group. *Eur J Cancer*. 1979;15:1033–1041.